REMARKS

Claims 1-18 and 21-28 remain in this application. Claims 1, 7, 8, 9, 10 and 18 have been amended to more particularly point out and distinctly claim that which the Applicants regard as the invention. More specifically, claim 1 has been amended to incorporate a functional limitation that is described throughout the specification, and also found in amended claim 10. Further, dependent claims 7-9 have been amended to read on the composition of matter recited in the independent claim 1; claim 10 has been amended so that it is now in independent form, and has merely incorporated the limitations of claim 1 from which it formerly depended from; claim 18 has been amended to correct its dependency from claim 1 to amended claim 10; and no new matter is introduced by any of the above amendments to the claims.

The Office Action notes informalities that require correction. These have been addressed by the above-made amendments to the specification. In particular, it is noted that the AGP-3 receptor sequence in Figure 18 is a variant of the receptor sequence shown in Figure 17 and SEQ ID NO:42 and the specification has been amended to denote the differences which are inherent to the sequence.

The specification has been amended to delete citation to PCT app. no. WO 99/25044 and it has been replaced with the proper International Publication Number WO 00/24782 (corresponding to International Application Number PCT/US99/25044). This reference was provided to the Office in a Supplemental IDS and Form 1449 on February 12, 2002. Consideration of the same is respectfully requested.

No new matter is added by these amendments as they are merely corrections of obvious typographical or clerical errors.

Furthermore, a substitute sequence listing has been submitted. This sequence listing amends the sequence shown as SEQ ID NO:43. The amended sequence corresponds to the extracellular domain of AGP-3 (SEQ ID NO:42) as described in the figure legend for Figure 18, and is not new matter.

Claims 10-18 are objected to under 37 C.F.R. 1.75(c) as being improperly dependent as they fail to further limit independent claim 1, from whence they depend. Attorney for Applicants does not agree and respectfully submits that a 'composition' as in claim 1 is typically construed as being more than two substances in a mixture (see, for example, pages 24-25 of the specification as filed). Here, a composition of matter is first, a polypeptide as shown by the representative variables, and second, at least one other compound. The dependent claims are drawn only to the polypeptide of the composition of claim 1.

Therefore the dependent claims are in fact narrower as they exclude the 'other compound(s)'. However, in order to expedite prosecution the application, claims 10-18 have been amended so that claim 10 is now an independent claim and claim 18 has been amended to depend from claim 10. It is respectfully submitted that the scope of the claims as a whole is unchanged and this objection overcome.

It is noted that claims 7-9 were also dependent from claim 1 and read on polypeptides, but were not found to be objectionable. Regardless, these claims have also been amended, without altering the scope of the overall claim protection, and are now consistent in format with the remaining claims.

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendments. The attached page is captioned **"Version With Markings To Show Changes Made."**

ARGUMENTS

A. 35 U.S.C. §112, First Paragraph

Claims 1-18, and 21-28 are rejected under 35 U.S.C. §112, first paragraph as lacking enablement. Specifically, it is alleged that it would require undue experimentation to practice the invention.

Attorney for Applicants respectfully traverses this rejection. It is noted that the amount of experimentation is not what determines whether the amount of experimentation is undue, rather it is the nature of the experimentation required. More specifically, the question to be asked is whether the experimentation is routine (see M.P.E.P. 2164.06)[1]. In *Ex parte Jackson*, 217 USPQ 804, the Board of Appeals referring to *Ansul v. Uniroyal*, 169 USPQ 759 (2d Cir. 1971) and *In re Rainer*, 146 USPQ 218 (CCPA 1965) pointed out that: 'determination of what constitutes undue experimentation in a given case requires the application of a standard of reasonableness having regard to the nature of the invention. ***The test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine*** or if the specification in question provides a reasonable amount of guidance with respect to the direction in which experimentation should proceed to enable determination of how to practice a desired embodiment of the invention claimed' (emphasis supplied).

[1] Time and difficulty of experiments are not determinative if they are merely routine. Quantity of examples is only one factor that must be considered before reaching the final conclusion that undue experimentation would be required. *In re Wands*, 858 F.2d at 737, 8 USPQ2d at 1404.

Here, the specification provides detailed description of the polypeptides and compositions of matter of the claims. The specification also teaches that the cysteine rich sequences of SEQ ID NOS: 45 and 46 are important for ligand/receptor binding (page 12, line 10 to page 13, line 2). In addition, the specification teaches how one can make various modifications to the polypeptides to develop alternative sequences that function as a binding partner to AGP-3 (see generally, pages 11-25). The changes can be made by routine mutagenesis, the polypeptides expressed by routine expression systems, and the activity of the polypeptides can be tested in routine assays, all of which are taught by the Applicants in the present specification.

In addition, in order to fit within the confines of the amended claim, the composition or polypeptide must be capable of binding AGP-3. This binding activity results in amelioration of B cell activation as described in the specification. The measuring of these activities by the assays taught in the specification are routine, and would exclude any molecules that lack the activity regardless of their structural differences (see, for example, pages 30-34). As there is no rule against defining molecules partly by their activity, it is respectfully submitted that the structural limitations in combination with the limitation regarding the activity (which can be tested by the routine assays as described) of the molecule would not require undue experimentation to practice the invention.

Furthermore, there is extensive teaching in the present specification on how to make polypeptides, peptides and muteins, that would function as binding partners of AGP-3. Much of this teaching is prophetic, however, the Patent and Trademark Office (PTO) itself has stated in M.P.E.P. §2164.01(c), quoting a Federal Circuit decision, that prophetic examples are acceptable.[2] It is well accepted that the binding domain of a TNF receptor like molecule resides in the cysteine rich domain. The claims require the presence of the cysteine rich region to be inclusive of an AGP-3 binding partner. Thus, it is respectfully submitted that even without working examples, the present invention has satisfied the enablement requirement.

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[2] *In re Chilowsky*, 229 F.2d 457, 461, 108 USPQ 321, 325 (CCPA 1956) ("The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it."); *In re Wooddy*, 331 F.2d 636, 639, 141 USPQ 518, 520 (CCPA 1964) ("It appears that no one on earth is certain as of the present whether the process claimed will operate in the manner claimed. **Yet absolute certainty is not required by the law.** The mere fact that something has not previously been done clearly is not, in itself, a sufficient basis for rejecting all applications purporting to disclose how to do it."). (emphasis supplied)

Consequently, it is respectfully submitted that the present specification is fully enabled for the scope of the claims and the invention can be practiced without undue experimentation, and withdrawal of this rejection is requested.

B. 35 U.S.C. §112, Second Paragraph

Claims 10-18 are rejected under 35 U.S.C. §112, second paragraph as being indefinite. Specifically, it is alleged that claim 1, from which the rejected claims depend, is directed to a composition of matter and the dependent claims are directed to polypeptides, thus there is an insufficient basis for these limitations. As discussed above in the remarks section, these claims have been amended such that claim 10 is now an independent claim and claim 18 is dependent from claim 10. Therefore it is respectfully submitted that this rejection has been overcome.

C. 35 U.S.C. §102(b)

Claims 1-18 and 21-28 are rejected under 35 U.S.C. §102(b) as being anticipated by Bram et al., WO 98/39361 ("the Bram reference"). The Bram reference teaches a polypeptide called TACI, which is the same as the polypeptide depicted in SEQ ID NO:42 in the instant specification. The Bram reference also teaches the extracellular, transmembrane and intracellular domains of TACI, and that fusions can be made of such domains with heterologous polypeptides including with Fc portions of antibodies, with the Fv domain of antibodies, among others (pages 26-27).

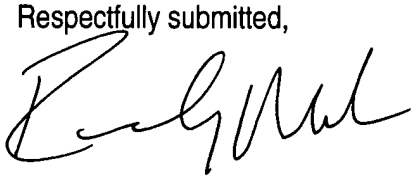
The Bram reference does not teach 'compositions of matter' as taught and claimed by the present specification. In particular, the Bram reference does not teach any fragments of TACI other than the extracellular, transmembrane and intracellular domains. Indeed, the present invention claims compositions that do not comprise SEQ ID NO:43, namely, the extracellular domain described in the Bram reference. Further, as amended, the present claims provide polypeptides and compositions that include SEQ ID NOS: 45 and 46 so long as any linker between these last two sequences is not a naturally occurring sequence between them that is found in SEQ ID NO:42. This hybrid polypeptide, as currently taught and claimed in the instant specification as filed, is not taught or suggested in the Bram reference. Thus, in light of the amendments to claims 1-18 and the above arguments, it is respectfully submitted that the Bram reference does not anticipate the subject claims.

In addition, the Bram reference does not teach that a portion of the extracellular domain of SEQ ID NO:42, not including SEQ ID NO:43, can be fused in frame to replace the CDR's of an antibody. Rather, the Bram reference only teaches that a fragment of the TACI molecule can be fused to an Fc or Fv fragment of an antibody. The purpose of fusing it to an Fv domain being to target TACI to a particular cell type. In these embodiments, the Fv fragment would retain its native CDR's, in complete contrast to a molecule where the polypeptide of the invention would be substituted into the CDR's. Alternatively, the Bram reference teaches a fusion of an Fc domain to a TACI fragment, however, this again does not constitute a replacement of CDR's of an antibody, which is an entirely different proposition. Thus, it is respectfully submitted that the assertion that the Bram reference anticipates claims 21-28 is in error and withdrawal of this rejection is respectfully requested.

CONCLUSION

It is respectfully submitted that the presently pending claims are now in form for allowance and allowance is earnestly requested. Should a telephone call help facilitate prosecution of this application, the Examiner is encouraged to telephone the undersigned attorney at the number listed below.

Respectfully submitted,



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Version With Markings To Show Changes Made

In the specification:

The specification has been amended as follows:

Replace paragraph 1 on page 9 with the following:

A. Increased B cell viability in AGP-3 transgenic mice. B cells were isolated from spleens of 3 month old AGP-3 transgenic mice (n-3) and control littermates (n=3). A total of $2.5x10^5$ B cells was aliquoted per well in a 96-well round bottom plate and incubated for 9 days. At the indicated days, cells were incubated with 5 ~~•g~~μg/ml Propidium Iodide and subject to FACS analysis for positive staining cells. Values are expressed as Mean ± SEM.

Replace paragraph 2 on page 9 with the following:

B and C. AGP-3 stimulates B cell proliferation. Purified B cells (10^5) from B6 mice were cultured in triplicates in 96 well plate with indicated amount of AGP-3 at the absence ~~(upper panel)~~(panel B) or presence of 2 ~~•g~~μg/ml anti-IgM antibody ~~(lower panel)~~(panel C) for a period of 4 days. Proliferation was measured by radioactive ^{3}(H) thymidine uptake in last 18 hours of pulse. Data shown represent mean ± standard deviation of triplicate wells.

Replace paragraph 1 on page 10 with the following:

Figure 18 shows the protein sequence of human AGP-3 receptor having a deleted leucine at position 162 and deleted proline at position 253 of SEQ ID NO: 42. The extracellular domain (SEQ ID NO: 43) includes the N-terminal domain (top line shown in Figure 18, SEQ ID NO: 44) through two cysteine-rich repeats (labeled I and II, SEQ ID NOS: 45 and 46) to the end of the "stalk" region (SEQ ID NO: 47). The transmembrane domain (labeled TM, SEQ ID NO: 48) is underlined, and the intracellular domain (labeled IC, SEQ ID NO: 49) is also indicated.

Replace paragraph 2 on page 21 with the following:

Preferred molecules in accordance with this invention are Fc-linked AGP-3 R-related proteins. Useful modifications of protein therapeutic agents by fusion with the "Fc" domain of an antibody are discussed in detail in a patent application entitled, "Modified Peptides as Therapeutic Agents," U.S. Ser. No. 09/428,082, International Publication. No. WO ~~PCT appl. no. WO 99/25044,~~00/24782, which is hereby

incorporated by reference in its entirety. That patent application discusses linkage to a "vehicle" such as PEG, dextran, or an Fc region.

Replace paragraph 1 on page 57 with the following:

The AGP-3 receptor contains a probably hydrophobic transmembrane domain that begins at a T166 and extends to L186. Based on this configuration relative to the methionine start codon, the AGP-3 receptor is predicted to be a type III transmembrane protein, with a N-terminal extracellular domain, a transmembrane region and a C-terminal intracellular domain. Unlike most other TNFR receptor family members, AGP-3 receptor contains two cysteine rich repeats within its N-terminal extracellular domain (Figure ~~4).~~ 17).

In the claims:

Claims 1, 7-10 and 18 have been amended as follows:

1. (Amended) A composition of matter comprising the structure

$$(X^1)_a\text{-}F^1\text{-}(X^2)_b$$

wherein:

F^1 is a vehicle;

X^1 and X^2 are each independently selected from $-(L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2$, $-(L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2\text{-}(L^3)_e\text{-}P^3$, and $-(L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2\text{-}(L^3)_e\text{-}P^3\text{-}(L^4)_f\text{-}P^4$

P^1, P^2, P^3, and P^4 are each independently selected from SEQ ID NOS: 45 and 46;

L^1, L^2, L^3, and L^4 are each independently linkers that are not naturally occurring amino acid sequences found in SEQ ID NO:42; and

a and b are each independently 0 or 1, provided that at least one of a and b is 1;

c, d, e, and f are each independently 0 or 1, provided that if P^1 is SEQ ID NO: 45 and P^2 is SEQ ID NO: 46, then d is 1;

~~and~~ wherein said composition of matter does not comprise SEQ ID NO: 43, and is capable of binding AGP-3.

7. (Amended) The ~~polypeptide~~ composition of matter of Claim 1, wherein F^1 is a water-soluble polymer or a carbohydrate.

8. (Amended) The ~~protein~~ composition of matter of Claim 7, wherein the polymer is polyethylene glycol.

9. (Amended) The ~~protein~~ composition of matter of Claim 7, wherein the carbohydrate is dextran.

10. (Amended) A polypeptide ~~of Claim 1~~ comprising the structure

$$(X^1)_a\text{-}F^1\text{-}(X^2)_b$$

wherein:

F^1 is a vehicle;

X^1 and X^2 are each independently selected from $-(L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2$, $-(L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2\text{-}(L^3)_e\text{-}P^3$, and $-(L^1)_c\text{-}P^1\text{-}(L^2)_d\text{-}P^2\text{-}(L^3)_e\text{-}P^3\text{-}(L^4)_f\text{-}P^4$

P^1, P^2, P^3, and P^4 are each independently selected from SEQ ID NOS: 45 and 46;

L^1, L^2, L^3, and L^4 are each independently linkers that are not naturally occurring amino acid sequences found in SEQ ID NO:42; and

a and b are each independently 0 or 1, provided that at least one of a and b is 1;

c, d, e, and f are each independently 0 or 1, provided that if P^1 is SEQ ID NO: 45 and P^2 is SEQ ID NO: 46, then d is 1;

wherein said polypeptide does not comprise SEQ ID NO: 43, and is capable of binding AGP-3~~capable of eliciting B cell growth, survival, or activation in mesenteric lymph nodes~~.

18. (Amended) A pharmaceutical composition comprising a therapeutically effective amount of a protein of Claim ~~1~~10 in a pharmaceutically acceptable carrier, adjuvant, solubilizer, stabilizer and/or anti-oxidant.